Nitazoxanide
Paul Hoffman

Nitazoxanide is a broad-spectrum drug manufactured by Romark Laboratories marketed under the trade name of 'Alinia'. The activity of nitazoxanide has been reported to go far beyond the FDA-approved treatment of cryptosporidiosis and giardiasis. The USDA has approved the drug for *Sarcocystis neurona* and off-label uses include treatment for helminth infection, *Trichomonas, Entamoeba, Clostridium difficile,* and viruses such as hepatitis C.

Nitazoxanide is a structural analog of thiamine pyrophosphate, and as such acts as an inhibitor of pyruvate:ferrredoxin oxidoreductase (PFOR) that converts pyruvate and CoA to acetyl CoA. Humans and many bacteria (such as *E. coli*) utilize pyruvate dehydrogenase (PDH) for this reaction, and therefore are not inhibited by nitazoxanide. Nitazoxanide shows high levels of activity against both metronidazole-sensitive and resistant *Trichomonas vaginalis* , with the greatest activity *in vitro* being observed when organisms are cultured under anaerobic conditions where PFOR plays a leading role in metabolism. Studies on the electron transfer activity of PFOR *in vitro* in the presence of nitazoxanide showed reduction in electron transfer in *T. vaginalis, E. histolytica, G. intestinalis, C. difficile, C. perfringens,* and *H. pylori.* The inhibitory action of nitazoxanide is through reversing the binding of pyruvate to enzyme-bound thiamine pyrophosphate (TPP), of which it is a structural analog. The bioactivity of nitazoxanide is pH dependent, and the protonated form is inactive. Despite widespread clinical use, no resistance has emerged to nitazoxanide, although resistance is theoretically possible through mutations in PFOR that maintain activity and TPP binding, but not binding by nitazoxanide. Nitazoxanide may be the first of a new class of antimicrobial drugs that inhibit function of a cofactor, rather than by inhibiting enzyme action.

Remaining research questions include establishing the molecular mechanism by which nitazoxamide inhibits helminths, since these parasites lack PFOR. The activity against viruses, if it is real, also remains unexplained. In addition, the experience with nitazoxamide provides an experimental drug discovery system that might be particularly appropriate for the development of therapeutics for use with intestinal pathogens, since activity within the lumen and minimal intestinal uptake would be advantageous from a toxicity standpoint.